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Sir:

Enclosed is a certified copy of European Patent Application No. 01301955.9. This application is recited in the declaration of this application, as filed.

The claim for priority made under 35 U.S.C. §119 made in the declaration is reiterated.

Specific acknowledgment of the receipt of these documents and of applicant's claim for priority is respectfully requested.

Respectfully submitted,

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Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

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Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

A method for non-invasively determining conditions in the circulatory system of a subject

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A METHOD FOR NON-INVASIVELY DETERMINING CONDITIONS IN THE CIRCULATORY SYSTEM OF A SUBJECT

BACKGROUND OF THE INVENTION

The present invention relates to an improved method for non-invasively determining a condition in the circulatory system of a subject. More particularly, the present invention is directed to non-invasively determining the functional cardiac output of the heart and the CO_2 partial pressure of venous blood. With the method of the present invention, these conditions can be determined on a breath-by-breath basis.

The physiological function of the heart is to circulate blood through the circulatory system to the body and lungs. For this purpose, the heart receives blood in arterial chambers during its relaxed or diastolic phase and discharges blood from its ventricle chambers during the contractile or systolic phase. The amount of blood discharged from a ventricle chamber of the heart per unit time is the cardiac output (CO). A typical cardiac output for the heart of a normal adult (at rest) is 5-6 liters per minute.

During circulation through the body, the blood is depleted of oxygen (O_2) and is enriched with carbon dioxide (CO_2) as a result of the metabolic activity of the body. A major purpose for blood circulation is to take venous blood that has been depleted in O_2 and enriched in CO_2 as a result of its passage through the tissues of the body and supply it to the lungs. In the alveoli of the lungs, O_2 is supplied to the blood from the breathing gases, typically air, and CO_2 is discharged into the breathing gases. The oxygenated arterial blood is then supplied to the body tissues. The gas exchange takes place in the capillaries of the lung because of the differences in concentration, or partial pressure, of O_2 and CO_2 in breathing gases, such as air, and in the venous blood. That is, the blood is low in O_2 and high in CO_2 whereas air is high in O_2 and low in CO_2.

To carry out the foregoing gas exchanges in the body and lungs of a subject, the heart is divided into a right side and a left side. The right side of the heart receives venous blood and pumps it to the lungs for oxygenation and CO_2 reduction. The left side of the heart receives the oxygenated blood from the lungs and supplies it to the arteries of the body for circulation through the tissue of the body. The cardiac output of the right and left sides of the heart is generally equal.

The regulatory mechanisms of the body respond to variations in metabolic

needs of body tissue by varying the cardiac output of the heart and the amount of gas exchange occurring in the lungs to maintain a sufficient supply of oxygen to body tissue and removal of CO_2 from body tissue. The CO_2 content of the blood is an indicator of the sufficiency of gas exchange occurring in the lungs. The gas exchange occurring in the lungs depends both on the amount of blood passing through the lungs, i.e. on the cardiac output (CO), and on the amount and efficiency of gas exchange occurring in the lungs. The amount of gas exchange can be grossly altered by changing the tidal volume of the lungs, as for example, by deep breathing. However, the amount of gas exchange, and particularly the efficiency of gas exchange, also depends on the physiological condition of the lungs.

A common condition reducing the gas exchange efficiency of the lungs is the presence of shunt perfusion or blood flow in the lungs. A shunt comprises pulmonary blood flow that does not engage in gas exchange with breathing gases, due to blockage or constriction in alveolar gas passages, or for other reasons. This shunt blood flow thus bypasses normal alveoli in which gas exchange is carried out. Upon leaving the lungs, the shunt blood flow mixes with the non-shunt blood flow. The former reduces the oxygen content and increases the CO_2 content in the mixed arterial blood supplied to the body tissues.

It will be appreciated that only the non-shunt pulmonary blood flow through the lungs participates in the gas exchange function of the lungs and in oxygenation and CO_2 removal in the blood of the subject. The quantity of blood that participates in such pulmonary gas exchange in the lungs is termed functional cardiac output (FCO). For diagnostic or other purposes, it is frequently desirable or essential to know this quantity.

While shunt conditions can occur in the lungs due to blockage brought about by disease, mechanical ventilation, particularly when the respiratory muscles of a subject are relaxed as during anesthesia, can result in an increase in the pulmonary shunt. The breathing gases supplied to the lungs can be enriched with oxygen under such conditions to assist in oxygenation of the blood. However, a sufficient amount of CO_2 may not be removed from the blood when the pulmonary shunt is increased, giving rise to potentially adverse consequences to the subject.

The classic technique for determining the functional cardiac output of the

heart is through use of the Fick equation.

$$FCO = \frac{VCO_2}{CvCO_2 - CcCO_2} \qquad (1)$$

where, VCO_2 in ml/min. is the amount of CO_2 released from the blood in the circulatory system of the subject,

CvCO2 is the mixed venous blood CO_2 content, for example in ml CO_2/ml of blood, and

$CcCO_2$ is the end capillary blood CO_2 content, i.e. the CO_2 content in the blood leaving the ventilated lungs.

The Fick equation states that, knowing the amount of CO_2 gas released from the blood in a unit of time (e.g. the rate of gas transfer as a volume/minute) and the concurrent gas transfer occurring per unit of blood (i.e. volume of gas/volume of blood), the blood flow through the lungs (i.e. FCO expressed in volume/minute) can be determined.

If a portion of the pulmonary blood flow of the subject is in shunt, this will decrease the amount of CO_2 released from the blood and the computation of Equation (1) provides an indication of the resulting decrease in functional cardiac output. In computing functional cardiac output using the Fick equation, the quantity VCO_2 can be determined non-invasively by subtracting the amount of CO_2 of the inhaled breathing gases, for example air, from the amount of CO_2 of the exhaled breathing gases, taking into account changes in the amount of CO_2 stored in the lungs and the deadspace in the breathing organs of the subject, such as the trachea and bronchi. The amount of CO_2 stored in the lungs can be computed from the alveolar CO_2 gas concentration, as determined from an end tidal breathing gas measurement, and the end expiratory volume V_{EE} of the lungs. The end capillary blood CO_2 content ($CcCO_2$) can be determined non-invasively, with a fair degree of accuracy, from a measurement of the concentration of CO_2 in the breathing gases exhaled at the end of the expiration of a tidal breathing gas volume, i.e. the end tidal

(ET) CO_2 level. The venous blood CO_2 content ($CvCO_2$), is often determined invasively. An alternate non-invasive approach for the determination of the $CvCO_2$ can be seen in U.S. Patent 6,042,550. In the approach, exhaled CO_2 enriched breathing gases are rebreathed by the subject in subsequent inhalations. As rebreathing of the exhaled breathings gases continues, breath-by-breath, the end tidal CO_2 partial pressure ($P_{ET}CO_2$) increases until the end capillary blood CO_2 partial pressure (P_cCO_2) is reached. At this point, it is postulated that the end tidal CO_2 partial pressure ($P_{ET}CO_2$), the alveolar CO_2 partial pressure (P_ACO_2), the end capillary blood CO_2 partial pressure (P_cCO_2), and the venous blood CO_2 partial pressure (P_vCO_2) are all equal and that this partial pressure can be converted to the venous CO_2 content ($CvCO_2$) for use in the Fick equation.

The need for the determination of the venous blood CO_2 content ($CvCO_2$) is eliminated by the use of a differential form of the Fick equation

$$FCO = \frac{VCO_2^N - VCO_2^R}{CcCO_2^R - CcCO_2^N} \qquad (2)$$

In the differential form of the Fick equation, the superscript N indicates values obtained in "normal" breathing conditions. The superscript R indicates values obtained during a short term "reduction" in the CO_2 partial pressure difference between that in the alveoli and that in the blood. This results in reduced CO_2 transfer in the lungs.

In using the differential form of the Fick equation, a first set of values for VCO_2 and $CcCO_2$ are obtained, as in the manner described above, under normal breathing conditions. These are identified by the superscript N. Thereafter, the amount of CO_2 in the breathing gases for the subject is increased. This maybe accomplished by a partial re-breathing of exhaled breathing gases. See U.S. Patent 5,836,300 and published International Patent Appln. WO 98/26710 that employ valve mechanisms for this purpose. Or, this may be accomplished by injecting CO_2 into the inhaled breathing gases as described in U.S. Patent 4,608,995.

The CO_2 enrichment increases the concentration of CO_2 in the alveoli in the lungs and reduces the CO_2 partial pressure difference between that of the breathing gases in the lungs and that in the venous blood. As noted above, it is that CO_2 partial pressure

difference that drives the CO_2 gas transfer from venous blood to the breathing gases in the alveoli of the lungs. The reduced CO_2 partial pressure difference reduces CO_2 gas transfer in the lung and causes an elevation of the CO_2 content in the blood downstream of the lung, i.e. in the arterial blood of the subject. In the time interval before the blood with elevated CO_2 content circulates through the body and returns to the lungs, the CO_2 content of venous blood ($CvCO_2$) entering the lungs can be taken to be the same for both the initial, normal breathing conditions (N) and the subsequent, reduced CO_2 partial pressure difference conditions labeled by the superscript R. This similitude permits the factor $CvCO_2$ to be dropped out of the Fick equation when expressed in the differential form as Equation 2 so that the cardiac output is determined by the ratio of the change in released CO_2 amounts (VCO_2) between the normal (N) and reduced (R) gas exchange conditions to the corresponding change in the end capillary blood CO_2 content ($CcCO_2$) in the normal and reduced (R) gas exchange conditions. The need to determine the venous blood CO_2 content ($CvCO_2$) from the subject is thus eliminated.

The foregoing approach is also advantageous with ventilated or anesthetized subjects since the alteration of the CO_2 content of the breathing gases can be effected by altering the ventilation provided to the subject. In the case of a subject anesthetized with a breathing circuit of the recirculating type, the alteration in CO_2 content may be carried out by bypassing the CO_2 absorber in the breathing circuit to increase the amount of CO_2 in the breathing gases that are recirculated to the subject for inspiration.

While the above described techniques avoid the need to invasively determine venous blood CO_2 content, other problems are created. Each time the cardiac output of the heart is measured, the CO_2 content of the blood is increased. This is particularly true in procedures in which the subject rebreathes only exhaled breathing gases, i.e. "total rebreathing" since there is a corresponding blockage of CO_2 removal or "washout" from the lungs of the subject. If the gas exchange capability of the subject's lungs is impaired, this exacerbates the problem of removing adequate amounts of CO_2 from the blood of the subject, particularly if the measurements are carried out frequently. A period of time is required for CO_2 levels in the venous and arterial blood of the subject to return to normal levels. This limits and prolongs the intervals between which functional cardiac output measurements can be taken.

Also, in cases in which a subject is being provided with a fixed volume of breathing gases, an increase in inspired CO_2 volume is accompanied by a decreased volume of inspired oxygen. This may produce an undesired reduction in the oxygen content in the blood or require increased oxygen concentrations in the inspired breathing gases, following a cardiac output measurement, to restore oxygen levels in the blood to desired values.

The problem of limits in rapidity with which measurement can be taken may be overcome by the technique described in published PCT application WO 00/42908. This document discloses a method for breath-by-breath determination of cardiac output and blood gas related parameters. The method is based on simultaneous measurements of oxygen and carbon dioxide quantities and the breathing gas flow. From these measurements, the instantaneous respiratory quotient (RQ) is calculated as well as the respiratory quotient integrated for a whole expiration made by the subject. The respiratory quotient (RQ) of the subject is the volume of CO_2 exhaled by the subject divided by the volume of O_2 inhaled by the subject. The expired CO_2 concentration at the moment the instantaneous respiratory quotient (RQ) has the value of 0.32 is then interpreted as the venous blood CO_2 partial pressure (P_vCO_2). When the instantaneous respiratory quotient (RQ) equals the average respiratory quotient (RQ) for the whole expiration, the CO_2 concentration is identified as the arterial blood CO_2 partial pressure (P_aCO_2). The CO_2 partial pressures thus obtained are then converted to blood gas content. Putting these blood gas contents and the amount of CO_2 released from the blood (VCO_2) in the non-differential form of the Fick equation, Equation 1, gives the functional cardiac output.

A shortcoming of this approach is that the measurement is based on respiratory quotients (RQ) experientially obtained from a group of subjects. Also, mean respiratory quotient (RQ) characteristics are not constant and may vary depending a number of circumstances, including diet. When a subject is ventilated, further variations even beyond usual limits transiently occur for up to an hour period when ventilation to the subject is changed.

Determination of the functional cardiac output through use of the Fick equations provides significant information regarding the amount of gas exchange occurring in the lungs of the subject. In addition to this information, it is often also desired

to relate lung gas exchange amounts and blood gas properties to the metabolic needs of the subject's body. If, for example, the gas exchange occurring in the lungs is insufficient as compared to the metabolic activity of the subject, CO_2 will accumulate in the subject's blood and the CO_2 content of the blood will rise. Clinicians may therefore wish to look at the levels of CO_2 and other gases in the blood of a subject. Thus, while the differential form of the Fick equation is designed to eliminate the need to measure CO_2 levels in venous blood when determining functional cardiac output, there may still exist a need for this information for other medical purposes.

Historically, CO_2 levels in venous blood have been obtained by invasively removing a blood sample from the subject and using a blood gas analyzer to analyze the gaseous properties of the blood sample. A blood gas analyzer typically expresses these properties as the partial pressures of the various gases in the blood. The use of partial pressures is based on Dalton's law which states that in a mixture of gases, such as O_2, N_2, CO_2, etc., in a container or in a medium, such as blood, the pressure exerted by each gas, i.e. its partial pressure, is the same as that which the gas would exert if it alone occupied the container or medium. This allows the partial pressure of a gas to serve as an expression of gas quantity. Physicians, and other clinicians, have become accustomed to seeing and working with blood gas properties expressed as partial pressures rather than as gas content expressed volumetrically or otherwise. Thus, while determination of functional cardiac output requires blood content, in many other instances it is desired to express blood gas properties as partial pressures. That is, an arterial CO_2 blood quantity could be expressed as a partial pressure, for example, $PaCO_2$, rather than as a content, $CaCO_2$, or a venous property could be expressed as a partial pressure as, $PvCO_2$, rather than as a content, $CvCO_2$.

However, in relating blood CO_2 contents and blood CO_2 partial pressures, there is often a failure to recognize that the levels of different gases in the blood are interrelated. Thus, the higher the O_2 level in the blood, the lower the capacity of the blood to transport CO_2. Stated in a different way, if the amount of CO_2 in the blood is to remain constant as the O_2 content of the blood changes, for example, increases, the CO_2 partial pressure must also change, i.e. also increase. This phenomenon is known as the Halldane effect and failure to take this effect into account will affect the accuracy by which, for

example, the CO_2 partial pressure of venous blood (P_VCO_2) can be determined from CO_2 blood content measurements obtained from the subject.

BRIEF SUMMARY OF THE INVENTION

An object of the present invention is to provide an improved method for non-invasively determining the functional cardiac output of a subject. A more particular object of the present invention is to provide a method for non-invasively determining functional cardiac output on a breath-by-breath basis so that such information is available to a clinician on a real time basis.

A further object of the present invention is to provide a method for simply and accurately determining CO_2 characteristics of the blood, such as the CO_2 partial pressure of venous blood ($PvCO_2$). Further, with the method of the present invention, characteristics, such as $PvCO_2$, can be determined on a breath-by-breath, real time, basis.

Another object of the present invention is to provide a method that can make such determinations in a manner that avoids the undue build up of CO_2 in the blood of the subject that has heretofore hindered such measurements.

Briefly, in accordance with one aspect of the improved method of the present invention, the amount CO_2 in the breathing gases exhaled by the subject and the end tidal (ET) CO_2 concentration of the exhaled breathing gases are measured. This is typically done for normal breathing by the subject and the measurements are labeled with an (N) for "normal." The normal breathing by the subject establishes a concentration of CO_2 in the lungs of the subject. Using the amount of CO_2 in the exhaled breathing gases, at least one value of the amount of CO_2 released from the circulatory system of the subject (VCO_2^N) is determined. Using the end tidal (ET) CO_2 concentration of the breathing gases exhaled by the subject at least one value of the end capillary blood CO_2 content of the subject ($CcCO_2^N$) or a quantity indicative of same is also determined.

The concentration of CO_2 in the lungs of the subject is then changed or altered. This may be accomplished by increasing the CO_2 content of the breathing gases inhaled by the subject. This increases the CO_2 concentration in the lungs of the subject, reducing CO_2 gas exchange in the lungs of the subject. The amount of CO_2 and the end

tidal (ET) CO_2 concentration of the breathing gases exhaled by the subject is measured for at least one breath of the subject under these conditions and the measurements labeled with an (R) for "reduced" gas exchange. From these measurements, a value for the amount of CO_2 released from the circulatory system of the subject (VCO_2^R), and a value for the end capillary blood CO_2 content ($CcCO_2^R$) of the subject or quantity indicative of same are obtained in the same manner as the N values. The R values are determined from gas measurements from a time period less than that required for blood leaving the lungs of the subject to pass through the circulatory system of the subject and return to the lungs.

A regression analysis is then performed using the obtained VCO_2^N, VO_2^R and $CcCO_2^N$, $CcCO_2^R$ values for normal and reduced gas exchange breathing to establish a regression line. The slope of the regression line represents the functional cardiac output (FCO) of the subject, as determined by a differential form of the Fick equation.

Further in accordance with the present invention, the regression line is extrapolated to obtain a value for the end capillary blood CO_2 content ($CcCO_2$), or quantity indicative of same, when the amount of CO_2 released from the circulatory system of the subject (VCO_2) is zero. Under conditions in which no CO_2 is released from the circulatory system of the subject, the CO_2 content of venous blood will be the same as that of the end capillary blood ($CcCO_2$), so that the former quantity ($CvCO_2$) now becomes known from the latter quantity. The venous blood CO_2 content ($CvCO_2$) thus determined can be inserted in the Fick Equation 1, along with the VCO_2 values and $CcCO_2$ values measured from the subject's subsequent normal breathing to compute the functional cardiac output of the subject.

Due to the CO_2 buffering action of the subject's body, the CO_2 content of venous blood remains relatively constant or changes only slowly with time. This allows the value for the CO_2 content of venous blood ($CvCO_2$) determined in the above manner to be used to ascertain the functional cardiac output of the subject for subsequent breaths of the subject on a breath-by-breath basis by solving the Fick Equation 1 using newly obtained values for VCO_2 and $CcCO_2$ measured in the subsequent breaths.

The accuracy by which these subsequent determinations can be made can

be improved by adjusting or calibrating the $CvCO_2$ value based on values for $CcCO_2$ obtained from measurements taken in subsequent breaths. To this end, a relationship is established between the value for $CvCO_2$ determined in the above manner and the value for $CvCO_2^N$ used in the linear regression and extrapolation that establishes that $CvCO_2$ value. The relationship established may be a ratio or a difference. The relationship is then applied to values of $CcCO_2$ obtained from subsequent breaths to correspondingly alter the $CvCO_2$ value. The new, altered, value for $CvCO_2$ is then used in the Fick Equation 1, along with VCO_2^N and $CcCO_2^N$ values obtained from the subsequent breaths to determine functional cardiac output with improved accuracy.

The invention has been described, above, in an embodiment in which the alteration in lung CO_2 concentration needed to establish the data points used in the regression analysis has been obtained by changing the concentration from a lower concentration to a higher concentration. That is, the lung CO_2 concentration existing in normal (N) breathing is increased by the reduced (R) lung gas exchange conditions. However, it is also possible to practice the method of the present invention in a manner in which the lung CO_2 concentration is changed from a higher concentration to a lower concentration in order to establish the regression data points. For example, a subject with diseased lungs and breathing with a mechanical ventilator may often breath with reduced tidal air flows to reduce trauma to the lungs or thoracic cavity from movement of the lungs. This results in elevated lung CO_2 concentrations and reduced CO_2 gas exchange. Values for VCO_2 and $CcCO_2$ are obtained under these conditions. Thereafter, the ventilation of the subject's lungs is temporarily increased. This will lower the lung CO_2 concentration and increase CO_2 gas exchange. Values for VCO_2 and $CcCO_2$ are again obtained for use in the regression analysis.

Thus, the two sets of values used in the regression analysis can be obtained by either altering the lung CO_2 concentration from a lower value to a higher value or from a higher value to a lower value.

The method of the present invention has been described above using the end capillary blood content ($CcCO_2$) for exemplary purposes. However, since end tidal CO_2 concentration, the end capillary blood CO_2 content ($CcCO_2$), and the end capillary blood CO_2 partial pressure all bear a fixed relationship to each other, appropriate values

for any of these quantities can be used in the denominator of the Fick Equation 1, with appropriate coefficients, to solve the equation.

To determine the CO_2 partial pressure of venous blood ($PvCO_2$), the venous blood CO_2 content ($CvCO_2$), determined as described above, is altered in accordance with the amount of oxygen in the venous blood, to correctly indicate the CO_2 partial pressure of the venous blood. By using a $CvCO_2$ value which is adjusted or calibrated in accordance with subsequent $CcCO_2$ values, an accurate indication of the venous blood CO_2 content ($PvCO_2$) of the subject can be provided on a breath-by-breath basis.

Various other features, objects, and advantages of the invention will be made apparent from the following detailed description and the drawings.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING

In the drawing:

Fig. 1 is a graph showing data obtained from the breathing gases of a subject under normal breathing conditions and under conditions of reduced gas exchange in the lungs of the subject;

Fig. 2 is a graph showing the relationship between the CO_2 content of blood and the CO_2 partial pressure of blood;

Fig. 3 is a schematic diagram of apparatus suitable for practicing the method of the present invention; and

Fig. 4 is a graph incorporating Fig. 1 and showing data obtained in a modification of the method of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The basic principles on which the method of the present invention is based are as follows. For one or more normal (N) breaths of the subject, values are obtained for the amount of CO_2 released from the blood (VCO_2^N) and for a quantity indicative of the end capillary blood CO_2 content, for example $CcCO_2^N$. One or more values for the same quantities are obtained under conditions of reduced (R) gas exchange in the lungs of the subject, to comprise VCO_2^R and $CcCO_2^R$ values. The CO_2 content of the inhaled

breathing gases may be increased to obtain the latter values and thereafter reduced to that for normal breathing.

The normal (N) breathing values (N) and reduced (R) gas transfer values (R) are used as data points for a regression analysis, such as a linear regression analysis. Graphically, the data points may be plotted on a graph in which the end capillary CO_2 blood quantity values, such as $CcCO_2$, are scaled along the abscissa and values for the released amount of CO_2 (VCO_2) are scaled along the ordinate. Such a graph is shown in Fig. 1. For simplicity only, a single set of N and R data points are shown in Fig. 1 as points 10 and 12, respectively. The regression analysis produces a straight line 14 providing the best fit for the data points. In the simplified example shown in Fig. 1, this is a straight line intersecting the two data points. The downward slope of line 14 makes it clear that the greater the amount of CO_2 that is released in the exhalations of the subject, the less will be the end capillary blood CO_2 content of the subject.

It will also be appreciated that the slope of line 14 represents the functional cardiac output of the subject as expressed in the differential form of the Fick equation, Equation 2. That is, the difference between the amount of CO_2 (VCO_2) released under normal (N) conditions and that released under reduced (R) gas transfer conditions shown along the ordinate of Fig. 1 represents the numerator of Equation 2. The corresponding situation exists with respect to the difference in end capillary blood CO_2 content ($CcCO_2$) shown on the abscissa of Fig. 2 and forming the denominator of Equation 2. When Equation 2 is presented graphically in the manner shown in Fig. 1, the functional cardiac output thus determined will have a negative sign due to the transposition of the quantities forming the denominator of the equation.

In the method of the present invention, regression line 14 is extended or extrapolated to cross the abscissa of Fig. 1 along which the $CcCO_2$ values are graphed. This point is shown as point 16 in Fig. 1. Point 16 on the abscissa of the graph of Fig. 1, represents a state in which the amount of CO_2 released from the lungs (VCO_2) is zero and provides an indication of the end capillary blood CO_2 content ($CcCO_2$) under such conditions. In the example shown in Fig. 1, this end capillary blood content ($CcCO_2$) is approximately 536 ml per liter of blood.

Under conditions in which no CO_2 is released from the blood of the subject

to the alveolar breathing gases, the end capillary blood CO_2 content ($CcCO_2$) will equal the venous blood CO_2 content ($CvCO_2$). Knowing the venous blood CO_2 content ($CvCO_2$) enables the functional cardiac output (FCO) of the subject to be determined from Fick Equation 1 using this $CvCO_2$ value and VCO_2 and $CcCO_2$ values determined from the breathing of the subject.

Thus, by using the method of the present invention, the functional cardiac output can be determined by Fick Equation 1 without requiring the total rebreathing of exhaled breathing gas, as proposed in the '550 patent to obtain a value for $CvCO_2$. Total rebreathing results in the elevated CO_2 blood levels that may be harmful to the patient and must be lowered before the functional cardiac output can again be determined. Since a number of breaths are required to restore CO_2 content to normal levels, this limits the measurement interval and prolongs the interval between FCO measurements. It also avoids the problem that the oxygen content of the re-breathed gases may be reduced in order to maintain constant breathing gas volumes. This may reduce oxygen levels in the blood of the subject and may require increased oxygen concentration in the inspired breathing gases immediately following a cardiac output measurement to restore oxygen levels in the blood to desired levels. With the method of the present invention, the elevation in breathing gas and blood CO_2 levels need be no greater than that required to provide R values that enable the regression analysis to be accurately carried out.

Also, by knowing the venous blood CO_2 content ($CvCO_2$) it is possible to determine the venous blood CO_2 partial pressure ($PvCO_2$). This is done with the aid of the relationships set out in graphic form in Fig. 2. Fig. 2 presents blood CO_2 partial pressures on the abscissa as a function of blood CO_2 content on the ordinate. The quantities are labeled P_x and C_x to indicate that the curves in the graph can be used for both arterial as well as venous blood. Use of the present invention to analyze the gas properties of venous blood is particularly advantageous in view of the difficulties heretofore encountered in obtaining these properties and is thus described below for exemplary purposes.

Blood CO_2 content is affected by the O_2 content of the blood, a circumstance described as the Halldane effect. Thus, the higher the O_2 level in the blood, the lower the capacity of the blood to transport CO_2. Stated in a different way, if the

amount of CO_2 in the blood is to remain constant as the O_2 content of the blood changes, for example, increases, the CO_2 partial pressure must also change, i.e. also increase. If the CO_2 partial pressure for venous blood is to be accurately determined, the foregoing circumstance prevents simple substitution of $CvCO_2$ for $PvCO_2$ due to the errors introduced by the Halldane effect.

The steps of the present invention shown in Fig. 2 enable the CO_2 partial pressure of the blood to be accurately established from the CO_2 content of the blood. In the graph of Fig. 2, the blood CO_2 content, such as $CcCO_2$, is shown on the ordinate. This is the same quantity that is scaled on the abscissa of the graph of Fig. 1. The abscissa of the graph of Fig. 2 is scaled in blood CO_2 partial pressure. The lines 18, 20, 22 in the graph of Fig. 2 relate blood CO_2 content to blood CO_2 partial pressure for various oxygenation conditions in the blood. It is convenient to express blood oxygenation as oxygen saturation of the hemoglobin (Hb) in the blood (SO_2). Hemoglobin is found in the red corpuscles of the blood and serves to carry oxygen from the lungs to the body tissues. The lines 18, 20, and 22 can be established using known medical data relating blood CO_2 content to blood CO_2 partial pressures for various oxygen levels in the blood. See, for example, *Respiratory Physiology*, by J. F. Nunn, published 1993 by Butterworths. Or the relationships expressed by lines 18, 20, and 22 may be determined experimentally from blood samples. Line 18 shows the $CxCO_2$ - $PxCO_2$ relationship when arterial blood has 100% hemoglobin oxygen concentration (SO_2). Line 20 is used to establish the relationship between blood CO_2 content ($CxCO_2$) and blood CO_2 partial pressure ($PxCO_2$) when the blood is at 65% oxygen saturation and line 22 is used when the blood is at 30% oxygen saturation. It will be appreciated that lines can be established for all desired oxygenation conditions of the blood.

In Fig. 2, point 16 shown on the abscissa of Fig. 1 has been transposed to the ordinate of Fig. 2 and again shown as point 16. The graph of Fig. 2 thus becomes one relating the venous blood CO_2 content ($CvCO_2$) (and end capillary blood CO_2 content ($CcCO_2$)) at zero CO_2 release (VCO_2) to the CO_2 partial pressure of venous blood ($PvCO_2$). The intersection of a horizontal line 24 drawn from point 16 in Fig. 2 to the appropriate curve in the graph of Fig. 2 and dropped to the abscissa by vertical line 26 will provide the CO_2 partial pressure in venous blood ($PvCO_2$) for the blood oxygen condition

represented by the curve. For example, when it is known that venous blood is at 65% hemoglobin oxygen saturation, the intersection of line 24 and curve 20 extended via line 26 to the abscissa of Fig. 2 will indicate the CO_2 partial pressure ($PvCO_2$) of the subject's blood to be about 6kPa.

The principles of the method of the present invention illustrate how the CO_2 content of venous blood ($CvCO_2$) can be determined from the end capillary blood CO_2 content ($CcCO_2$) at zero release of CO_2 from the blood of the subject, i.e. VCO_2 equals zero. It will be appreciated that if it is desired to determine the end tidal CO_2 concentration ($F_{ET}CO_2$) under zero CO_2 release conditions, the same principles as described above can be used simply by scaling the abscissa of Fig. 1 in end tidal CO_2 concentration and plotting N and R data using VCO_2 and $F_{ET}CO_2$ values. Further, since the CO_2 partial pressure of end capillary blood bears a known relation to the end tidal CO_2 concentration, the CO_2 partial pressure of end capillary blood ($PcCO_2$) at zero release of CO_2 from the blood of the subject can also be determined by applying the known relationship.

These other quantities, indicative of the end capillary blood CO_2 content, can also be used to determine the functional cardiac output of the subject using an equation of the Fick Equation 1 type in a manner analogous to that described above and applying appropriate coefficients to the end tidal CO_2 or end capillary blood CO_2 partial pressure values inserted in the equation.

Fig. 3 shows apparatus suitable for carrying out the method of the present invention using mechanical ventilating equipment. The breathing organs of the subject, including lungs 50 are supplied with breathing gases through breathing circuit 52 of conventional construction. Breathing circuit includes inspiration limb 54 that supplies breathing gases to the subject and expiration limb 56 that receives exhaled breathing gases from the subject. Inspiration limb 54 and expiration limb 56 are connected to two arms of Y-connector 58. A third arm of Y-connector 58 is connected to patient limb 60. Patient limb 60 supplies and receives breathing gases to/from the subject through an endotracheal tube, face mask, or other appliance (not shown).

The other ends of inspiration limb 54 and expiration limb 56 are connected to ventilator 62. Ventilator 62 provides breathing gases in inspiration limb 54 and

receives breathing gases from expiration limb 56.

In the usual manner of a breathing circuit, patient limb 60 contains various breathing gas sensing and other apparatus. Patient limb 60 may contain flow sensor 64 for measuring breathing gas flows to and from the subject. A flow measuring apparatus suitable for use in breathing circuit 52 is shown in U.S. Patent 5,088,332 to Instrumentarium Corp. of Helsinki, Finland. A hot wire anemometer may also be used for this purpose.

Patient limb 60 also contains quantitative gas sensing apparatus 66 for measuring the composition of the breathing gases to/from the patient. Such gas sensing apparatus includes a CO_2 sensor for measuring the amount of CO2 in the breathing gases and end tidal CO2 concentrations. The CO_2 sensor typically comprises apparatus using infrared radiation. Such equipment may comprise a gas monitoring module M-GAS made and sold by Datex-Ohmeda Division of Instrumentarium Corp. of Helsinki, Finland.

The output of sensors 64 and 66 are provided in sampling lines 65 and 67 to signal processing unit 68 in which integration of flow rates to obtain volumes, filtering, or other signal processing is carried out to produce values for the sensed quantities. Signal processing unit 68 is connected to calculation and control unit 70. The necessary integration, filtering, etc. of the signals from sensors 64 and 66 may be carried out in the calculation and control unit 70. Signal processing unit 68 may also include means for determining when inhalation by the subject commences. The flow sensor 64 or a pressure sensor may be used for this purpose to sense the incipient flow of breathing gas toward the patient or pressure change that characterizes the initiation of inhalation.

Fig. 3 shows apparatus in which the increased lung CO_2 concentrations in breathing gases are obtained by injecting CO_2 into the inhaled breathing gases. To this end, dosing apparatus 72 is connected to CO_2 supply line 74 to inject CO_2 into the breathing gases inhaled by the subject. Dosing device 72 is connected to a supply of CO_2 (not shown). CO_2 supply line 74 terminates in the flow path for the subject's breathing gases, downstream of sensors 64 and 66, as shown in Fig. 3. Dosing apparatus 72 may comprise apparatus of the type shown in U.S. Patents 5,918,596 and 6,131,572

owned by the Instrumentarium Corp. of Helsinki, Finland that enable the delivered amount of CO_2 to be accurately determined. Dosing apparatus 72 is connected to calculation and control unit 70 and the amount of CO_2 injected is determined by calculation and control unit 70. Dosing device 72 may provide dosing volume feedback data to calculation and control unit 70 for use in controlling the operation of dosing apparatus 72. Signal processing unit 68 provides a trigger signal to dosing apparatus 72 for initiating the administration of CO_2 during inhalation by the subject. Typically, this would be at the onset of the inspiration of breathing gases into the lungs of the subject. Or, a signal from ventilator 62 may be provided to dosing apparatus 72 for this purpose.

Calculation and control unit 70 contains a microprocessor or other suitable element for carrying out the technique of the invention described in connection with Figs. 1 and 2.

Sensors 64 and 66 and signal processing unit 70 measure gas flows, expired CO_2 concentrations, and end tidal CO_2 gas concentrations. Measured expired CO_2 concentrations and gas flows can be used to determine the amount of CO_2 (VCO_2) released from the blood. The end tidal CO_2 concentration is used to determine quantities indicative of the CO_2 content of the blood, such as $CcCO_2$, as described above.

The method for carrying out the method of the present invention is as follows. The method is described as in an instance using air as the breathing gases. Respiration may be either spontaneous on the part of the subject or assisted by the ventilation apparatus shown in Fig. 3.

The subject breathes, or is ventilated, with breathing gases such as air. The normal (N) breathing action of the subject is allowed to stabilize. This may, for example, require a minimum of five breaths or a half a minute to a minute of time. The amount of CO_2 released from the blood in the lungs of the subject and the CO_2 concentration in the breathing gases are then measured, for at least one breath, or preferably for each of a plurality of breaths, of the subject. Typically, the CO_2 concentration is measured as the end tidal CO_2 concentration ($P_{ET}CO_2^N$). One or more values of VCO_2 (N) are determined. In this exemplary description, the quantity used to describe the end capillary blood CO_2 condition is the CO_2 content ($CcCO_2$). The

measured end tidal CO_2 concentrations are thus used to determine $CcCO_2$ and one or more $CcCO_2$ N values are obtained from the end tidal CO_2 levels for the breaths.

Thereafter, the CO_2 content of the breathing gases inhaled by the subject is increased to increase the CO_2 concentration in the lungs of the subject and to reduce CO_2 gas transfer. Using the apparatus shown in Fig. 3, this may be accomplished by administering a bolus of CO_2 into the inhaled breathing gases each time the subject breaths. Or, the subject may engage in re-breathing of breathing gases previously exhaled by the subject.

The end tidal CO_2 levels are examined as the subject breaths under these conditions. When the end tidal CO_2 levels no longer change, this indicates that the alveolar CO_2 concentration in the lungs is constant which means that CO_2 storage in the lungs has been accommodated. The measurement of the amount of gas released from the lungs of the subject and CO_2 concentrations of the breathing gases, i.e. end tidal CO_2 concentration, is then commenced. After measurements are taken, the enrichment of CO_2 in the inhaled breathing gases may thereafter be terminated and CO_2 concentrations in the lungs allowed to return to normal levels.

The exact amount and duration of the CO_2 enrichment will depend on numerous physical and physiological factors of the patient and on the data needed to accurately determine functional cardiac output. For injected CO_2 the amount is typically 5 ml to 30 ml per breath occurring over several breaths, for example, those taken in 20 seconds to one minute in time. For a typical adult, CO_2 would be injected in about 6 or 7 breaths.

The amount of CO_2 provided in the boluses is governed by somewhat conflicting considerations. The larger the boluses, the larger will be the alveolar CO_2 concentration in the lungs and the end capillary blood CO_2 content ($CcCO_2$). This will place the R data point 12 closer to the intersection of line 14 with the abscissa of Fig. 1 at point 16 and improve the accuracy by which $CvCO_2$ can be determined. On the other hand, the more CO_2 that is delivered, the less CO_2 gas exchange occurs in the lungs of the subject resulting in higher CO_2 blood levels that require a longer time to return to normal levels. The amount of CO_2 delivered to the subject represents an optimum combination of these factors and need be no greater than that required to achieve the

desired results.

The amount of CO_2 released from the blood of the subject (VCO_2^R) is determined by subtracting the amount of CO_2 in the enriched, inhaled breathing gases from the CO_2 amount measured in the exhaled breathing gases. The measured end tidal CO_2 levels are used to determine the end capillary blood CO_2 content $CcCO_2^R$. These determinations are carried out from measurements obtained within the circulation period of the blood in the body of the subject following the administration of the boluses. This is a period of approximately 30 seconds to one minute. In this period, the venous blood CO_2 content ($CvCO_2$) remains constant since it has not yet returned to the lungs to undergo gas exchange.

If desired, an administration of increased CO_2 in the inhaled breathing gases to the subject can be repeated after an appropriate interval during which CO_2 levels in the blood return to normal.

A regression analysis, such as a linear regression analysis, is then performed using the normal (N) values obtained from the initial breaths of the patient and the reduced (R) gas transfer values obtained following the increase in the CO_2 content of the inhaled breathing gases. It will be appreciated that the data used to perform the regression analysis can include many normal (N) values obtained from the plurality of normal breaths taken by the patient. There will be a smaller number of R values since usually only one R value is obtained each time the CO_2 content of the inhaled breathing gas is increased.

As noted above, the slope of line 14 produced by the regression analysis is the negate of the functional cardiac output (FCO) of the patient.

The intersection of line 14 with the abscissa of Fig. 1 is then determined to provide an end capillary blood ($CcCO_2$) value for condition of zero CO_2 release (VCO_2) from the blood and the corresponding venous blood CO_2 content ($CvCO_2$).

The venous CO_2 content ($CvCO_2$) determined, as described above, is then used for further determination of the functional cardiac output by using the non-differential form of the Fick equation, Equation 1, above. To this end, the quantity $CvCO_2$ is inserted in Fick Equation 1. Measured CO_2 release (VCO_2) values and end capillary blood CO_2 ($CcCO_2$) values taken from subsequent breaths and representing

normal (N) values of these quantities are also inserted in Fick Equation 1 to compute of the functional cardiac output from these subsequent breaths.

The solution result of the Fick Equation 1 will remain accurate for as long as the determined value of $CvCO_2$ remains accurate. Since the body of the subject buffers changes in CO_2 in the body, this allows $CvCO_2$ to remain relatively constant for a useful period of time.

The accuracy of the value for venous blood CO_2 content ($CvCO_2$) used in solving Fick Equation 1 along with data from subsequent breaths of the subject, can be improved by adjusting or calibrating the value in the manner described below. These techniques are based on establishing a relationship between the value of venous blood CO_2 content ($CvCO_2$), determined as described above, and the normal (N) breathing end capillary CO_2 content ($CcCO_2^N$) used in that determination. This relationship is then used to adjust or calibrate the venous blood CO_2 content ($CvCO_2$) when new end capillary blood CO_2 content ($CcCO_2$) values are obtained from subsequent breaths of the subject.

For example, it will be seen from an inspection of Fig. 1 that a venous blood CO_2 content ($CvCO_2$) value of approximately 536 ml/l (the intersection 16 of line 14 with the abscissa of Fig. 1) is obtained when the normal (N) value for the end capillary blood CO_2 content ($CcCO_2$) is approximately 480 ml/l. This quantity is obtained by determining the X axis coordinate for normal N point 10 as shown by dotted line 80 in Fig. 1. Placing $CvCO_2$ in a numerator and $CcCO_2^N$ in a denominator provides a ratio between the two values, which in this example has a numerical value 1.13.

In the computation of functional cardiac output using Fick Equation 1, newly determined $CcCO_2^N$ values obtained from subsequent normal (N) breaths of the subject are multiplied by the quantity 1.13 to obtain new $CvCO_2$ values to be used in Fick Equation 1, thereby improving the accuracy with which functional cardiac output is determined.

Another technique that may be used in accurately solving Fick Equation 1 is as follows. Using the $CvCO_2$ value obtained in the manner described above, and illustrated in Fig. 1, and the corresponding X axis coordinate value for $CcCO_2^N$, the

difference between these values along the X axis is determined. In the numerical example shown in Fig. 1, the value for $CvCO_2$ is 536 ml/l and for $CcCO_2^N$ is 480 ml/l. The difference is 56 ml/l. Thereafter, this amount is applied to $CcCO_2^N$ values obtained in subsequent normal (N) breaths from the subject, i.e. the difference amount, such as 56, is added to the $CcCO_2^N$ values obtained from the subsequent breaths of the subject to obtain the new $CvCO_2$ values which are used in the solution of Fick Equation 1.

The second and third calibration techniques described above enables the $CvCO_2$ value to follow the $CcCO_2^N$ quantities obtained by measurements taken in the subsequent breaths of the patient. This improves the accuracy by which the functional cardiac output (FCO) of the subject can be determined.

To determine functional cardiac output on a breath-by-breath basis, the VCO_2 and $CcCO_2$ data obtained for each normal (N) breath of the subject is entered in Fick Equation (1), along with the $CvCO_2$ value determined in one of the various ways described above. The computation of functional cardiac output is then carried out using the data for that breath. The use of subsequently obtained normal (N) breathing end capillary blood CO_2 content ($CcCO_2^N$) to calibrate or adjust the venous blood CO_2 ($CvCO_2$) value used in Fick Equation 1 allows the functional cardiac (FCO) to be determined on a real time basis over an extended period of time. And, as noted above, this is accomplished without the undue increase the CO_2 content of the subject's blood that has occurred in the past.

If significant changes occur in the breathing conditions for the subject, for example, a change in the settings of ventilator 62, or in patient metabolism, or in disease status, the original steps of the method must again be carried out to obtain a new value for the venous blood CO_2 content ($CvCO_2$) to be used in the computation of functional cardiac output.

In the method described above, the alteration in the CO_2 concentration in the lungs necessary to obtain the regression analysis data points has been obtained by increasing the CO_2 lung concentration as a result of the subject breathing CO_2 enriched breathing gases. However, since what is needed in the method of the present invention is two different lung CO_2 concentrations to obtain the two data points, it is equally possible to practice the invention in a manner in which CO_2 lung concentrations are

reduced as the steps of the method are carried out. Such a method is illustrated in Fig. 4.

A subject may breath with reduced ventilation, typically characterized by reduced tidal volume and reduced frequency. This may occur naturally or as a result of mechanical ventilation and is often done to protect the lungs. The reduced ventilation reduces the amount of CO_2 (VCO_2) exhaled by the subject and increases the CO_2 concentration in the lung. This, in turn, reduces CO_2 gas exchange in the lung and increases end capillary blood CO_2 levels ($CcCO_2$). A data point produced from the VCO_2 and $CcCO_2$ measurements under these conditions is shown as point 100 in Fig. 4. To assist in the explanation, and for comparative purposes, Fig. 4 also shows the data of Fig. 1. Point 100 is analogous to an R value, i.e. is obtained under conditions of reduced gas transfer in the lungs.

To obtain the necessary alteration in lung CO_2 concentrations and gas transfer in the lungs required to produce another data point, the ventilation of the subject is increased, as by increasing the breathing tidal volume and/or respiration frequency. The increased ventilation, decreases lung CO_2 concentrations and increases CO_2 gas exchange in the lungs toward a more normal (N) condition. A data point produced from the VCO_2 and $CcCO_2$ measurements under these conditions is shown as point 102 in Fig. 4. The breathing of the subject may then revert to the former state.

The two data points are used in a regression analysis to produce line 104. In the example shown in Fig. 4, the slope of line 104 is the same as that of line 14, meaning that the functional cardiac output is the same for the two sets of conditions shown in Fig. 4. However, need not be, and usually will not be, the case. Line 104 intersects the abscissa of the graph of Fig. 4 at point 106. Due to the reduced CO_2 gas transfer in the lungs of the subject, as a result of the reduced ventilation of the subject, the end capillary blood CO_2 content ($CcCO_2$) at zero release of CO_2 from the blood of the subject indicated by point 106 will be higher than that indicated by point 16 in the example of Fig. 1. The venous blood CO_2 content (CvCO2), also indicated by point 106, will similarly be higher. The venous blood CO2 content so determined can be used in the Fick Equation 1 in the same manner as described above to determine the functional cardiac output.

The method of the present invention also allows venous blood CO_2 partial

pressure ($PvCO_2$) to be accurately determined on a breath-by-breath basis. For each normal (N) breath taken by the subject, an new value for the end capillary blood CO_2 quantity, such as content ($CcCO_2$), will be determined. From this quantity, a new venous blood CO_2 content ($CvCO_2$) is determined in one of the ways described above. This new $CvCO_2$ value is then used to enter the graph of Fig. 2 along the ordinate. The new venous blood CO_2 partial pressure ($PvCO_2$) can be determined from the abscissa of the graph Fig. 2 knowing the amount of oxygen in the blood. The present invention thus also makes venous blood CO_2 partial pressure ($PvCO_2$) available on a breath-by-breath basis.

It is recognized that other equivalents, alternatives, and modifications aside from those expressly stated, are possible and within the scope of the appended claims.

CLAIMS

1. A method for non-invasively determining a condition of the circulatory system of a subject, the subject inhaling and exhaling breathing gases during breathing, said method comprising the steps of:

(a) measuring the amount of CO_2 in the breathing gases exhaled by the subject and the CO_2 concentration of the breathing gases exhaled by the subject for a first (1) breathing condition of the subject;

(b) determining at least one value of the amount of CO_2 released from the circulatory system of the subject (VCO_2^1) using the amount of CO_2 in the breathing gases exhaled when the subject is in the first condition;

(c) determining at least one value for a quantity indicative of the end capillary blood CO_2 content of the subject using the CO_2 concentration of the breathing gases exhaled when the subject in the first condition;

(d) altering the CO_2 concentration in the lungs of the subject;

(e) measuring the amount of CO_2 in the breathing gases exhaled by the subject and the CO_2 concentration of the breathing gases exhaled by the subject for at least one breath of the subject under second (2) breathing conditions of altered CO_2 in the lungs of the subject;

(f) determining at least one value for the amount of CO_2 released from the circulatory system of the subject (VCO_2^2), the determination of the value being carried out in a time period less than that required for blood leaving the lungs of the subject to pass through the circulatory system of the subject and return to the lungs, the determination of the value using the amount of CO_2 in the exhaled breathing gases for the second breathing condition;

(g) determining at least one value for a quantity indicative of the end capillary blood CO_2 content of the subject, the determination of the value being carried out in a time period less than that required for blood leaving the lungs of the subject to pass through the circulatory system of the subject and return to the lungs, the determination of the value using the CO_2 concentration of the breathing gases exhaled for the second breathing condition; and

(h) performing a regression analysis using the determined VCO_2^1,

VO_2^2, and end capillary blood CO_2 quantity values to establish a regression line; and

(i) extrapolating the regression line to obtain a value for the end capillary blood CO_2 quantity when the amount of CO_2 released from the circulatory system of the subject (VCO_2) is zero.

2. The method according to claim 1 wherein steps (a) and (e) are further defined as measuring end tidal CO_2 concentrations of the breathing gases exhaled by the subject.

3. The method according to claim 2 further defined in that the quantity, for which values are determined in steps (c) and (g), comprises the end tidal CO_2 concentration of the exhaled breathing gases and that the value obtained in step (i) is the end tidal CO_2 concentration when the amount of CO_2 released from the circulatory system of the subject (VCO_2) is zero.

4. The method according to claim 1 further defined in that the quantity, for which the values are determined in steps (c) and (g), comprises the CO_2 partial pressure in the blood of the subject and that the value obtained in step (i) is the CO_2 partial pressure of the end capillary blood of the subject when the amount of CO_2 released from the circulatory system of the subject (VCO_2) is zero.

5. The method according to claim 1 or 2 further defined in that the quantity, for which the values are determined in steps (c) and (g), comprises the CO_2 content of the end capillary blood ($CcCO_2$) of the subject and that the value obtained in step (i) is the CO_2 content of the end capillary blood of the subject when the amount of CO_2 released from the circulatory system of the subject (VCO_2) is zero, which value comprises the CO_2 content of venous blood ($CvCO_2$).

6. The method according to claim 1, 2, 3, 4 or 5 further including the step of using the value obtained in step (i) to determine the functional cardiac output (FCO) of the subject using a non-differential form of the Fick equation.

7. The method according to claim 1, 2, 3, 4 or 5 further defined as including the steps of:

determining further values for the amount of CO_2 released from the circulatory system of the subject (VCO_2) and for the quantity indicative of the end capillary blood CO_2 content for breathing of the subject in the first breathing condition; and

using the value provided by the extrapolation of the regression line in step (i) and a further determined released CO_2 amount (VCO_2) and value for the quantity indicative of end capillary blood CO_2 content to determine the functional cardiac output of the subject using a non-differential form of the Fick equation.

8. The method according to claim 7 further defined as being carried out on a breath-by-breath basis.

9. The method according to claim 1, 2, 3, 4 or 5 further including the steps of:

determining a further value for the quantity indicative of the end capillary blood CO_2 content for breathing of the subject in the first breathing condition;

forming a relationship between the value for the quantity indicative of the end capillary blood CO_2 content for breathing in the first breathing condition used in the regression analysis and the value obtained by extrapolating the regression line in step (i); and

applying the relationship to the further determined value for a quantity indicative of the end capillary blood CO_2 content to provide a new value for the value which was obtained by the extrapolation of the regression line in step (i).

10. The method according to claim 9 further defined as forming a relationship comprising as a ratio.

11. The method according to claim 9 further defined as forming a

relationship comprising a difference.

12. The method according to claim 9, 10 or 11 further including the steps of:

determining further values for the amount of CO_2 released from the circulatory system of the subject (VCO_2^N) for breathing of the subject in the first breathing condition; and

using the further determined released CO_2 amount (VCO_2^1), the further determined value for a quantity indicative of the end capillary blood CO_2 content, and the new value for the value which was obtained by extrapolation of the regression line in a non-differential form of the Fick equation to determine the functional cardiac output (FCO) of the subject.

13. The method according to claim 9, 10, 11 or 12 further defined as being carried out on a breath-by-breath basis.

14. The method according to claim 1 wherein the step of altering the CO_2 concentration in the lungs of the subject is further defined as increasing the CO_2 concentration in the lungs of the subject to reduce CO_2 gas exchange in the lungs of the subject.

15. The method according to claim 14 wherein the step of increasing the CO_2 concentration in the lungs of the subject is further defined as increasing the CO_2 content of the breathing gases inhaled by the subject.

16. The method according to claim 15 further defined as administering a bolus of CO_2 into the breathing gas inhaled by the subject.

17. The method according to claim 15 further defined as causing the subject to inhale breathing gas previously exhaled by the subject.

18. The method according to claim 15 wherein step (d) is further defined as increasing the CO_2 by an amount which improves the accuracy of the determination while avoiding undue build up of CO_2 in the blood of the subject.

19. The method according to claim 1 wherein the step of altering the CO_2 concentration in the lungs of the subject is further defined as decreasing the CO_2 concentration in the lungs of the subject to increase CO_2 gas exchange in the lungs of the subject.

20. The method according to claim 19 wherein the step of decreasing the CO_2 concentration in the lungs of the subject is further defined as increasing the ventilation of the subject.

21. The method according to claim 5 further defined as including the steps of:

determining the amount of oxygen in the venous blood of the subject; and

altering the obtained value for the venous blood CO_2 content ($CvCO_2$) in accordance with the amount of oxygen in the blood to provide a CO_2 partial pressure value ($PvCO_2$) for venous blood.

22. The method according to claim 21 wherein the step of the determining the amount of oxygen in the venous blood is further defined as determining the degree of oxygen saturation of the venous blood.

23. The method according to claim 21 further defined as including the steps of:

determining a further value for the quantity indicative of the end capillary blood CO_2 content for breathing of the subject in the first breathing condition;

forming a relationship between the value for the quantity indicative of the end capillary blood CO_2 content for breathing in the first breathing condition used in the regression analysis and the $CvCO_2$ value obtained by extrapolating the regression line in

step (i);

applying the relationship to the further determined value for a quantity indicative of the end capillary blood CO_2 content to provide a new $CvCO_2$ value; and

altering the new $CvCO_2$ value in accordance with the amount of oxygen in the blood to provide a new CO_2 partial pressure value ($PvCO_2$) for venous blood.

24. The method according to claim 23 further defined as forming a relationship comprising a ratio.

25. The method according to claim 23 further defined as forming a relationship comprising a difference.

26. The method according to claim 21, 22, 23, 24 or 25 further defined as carrying out the method on a breath-by-breath basis.

27. The method according to claim 1 further defined as performing linear regression analysis using the VCO_2^1, VO_2^2, and 1 and 2 values for the quantity indicative of the end capillary blood CO_2 content of the subject.

28. The method according to claim 1 where the breathing gases supplied to the subject comprise air.

29. The method according to claim 1 further including the step of allowing the subject to take a sufficient number of breaths to stabilize the CO_2 content and CO_2 concentration of the exhaled breathing gases before taking the breathing measurements for the first breathing condition of the subject.

30. The method according to claim 1 further defined as determining a plurality of values for at least one of the amount of CO_2 removed from the lungs of the patient (VCO_2) and the quantity indicative of the end capillary blood CO_2 content for use in performing the regression analysis.

31. The method according to claim 1 wherein steps (b) and (f) are further defined as determining at least one value of the amount of CO_2 released from the circulatory system of the subject (VCO_2) using the CO_2 content of the inhaled and exhaled breathing gases.

ABSTRACT OF THE DISCLOSURE

A method for non-invasively determining functional cardiac output (FCO) and/or venous blood CO_2 partial pressure ($PvCO_2$). The amount of CO_2 (VCO_2^N) released from the blood and end capillary blood CO_2 content ($CcCO_2^N$) are determined from measurements from exhaled breathing gases. The CO_2 content of the breathing gases inhaled by the subject is increased to increase lung CO_2 concentration and reduce CO_2 gas exchange in the lungs of a subject. Values for VCO_2^R and $CcCO_2^R$ are obtained in a time period less than that required for blood recirculation in the body. A regression analysis is performed using the obtained VCO_2^N, VO_2^R, $CcCO_2^N$, and $CcCO_2^R$ values. The regression line is extrapolated to obtain a value for $CcCO_2$ when (VCO_2) is zero. Under this condition, the CO_2 content of venous blood ($CvCO_2$) will be the same as $CcCO_2$, so that $CvCO_2$ becomes known. The $CvCO_2$ thus determined can be inserted in a non-differential form in the Fick equation, along with VCO_2 and $CcCO_2$ values from normal breathing, to determine FCO. As the CO_2 content of venous blood remains relatively constant, FCO can be determined for subsequent breaths of the subject on a breath-by-breath basis using the determined $CvCO_2$ value and VCO_2^N and $CcCO_2^N$ values from the subsequent breaths. The accuracy of these subsequent determinations can be improved by calibrating $CvCO_2$ based on subsequent $CcCO_2$ values. To determine $PvCO_2$, $CvCO_2$ is altered in accordance with the amount of oxygen in the venous blood, to correctly indicate $PvCO_2$. By using a calibrated $CvCO_2$ value, $PvCO_2$ can be provided on a breath-by-breath basis. The method can also be practiced by reducing lung CO_2 concentrations and using values for VCO_2 and $CcCO_2$ obtaining before and after the reduction.

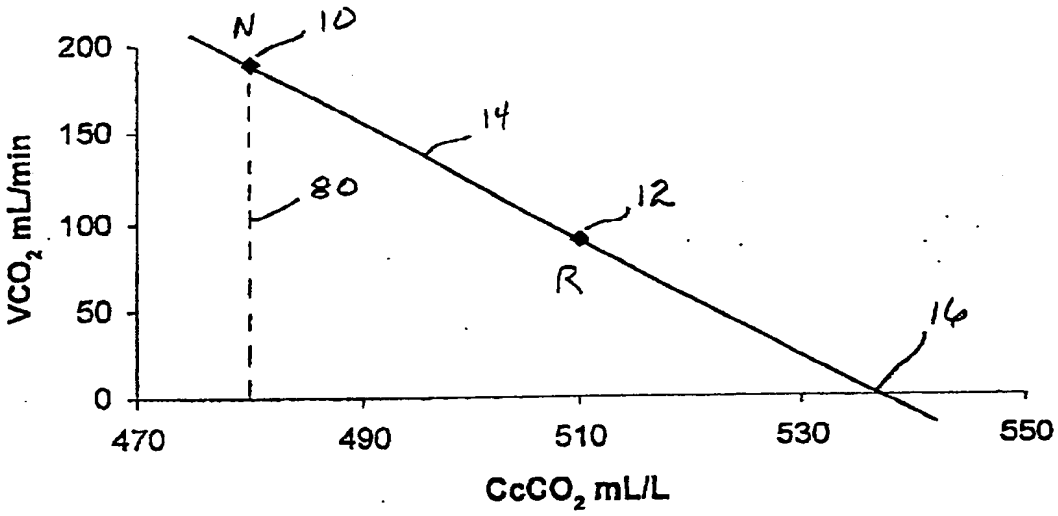


Figure 1

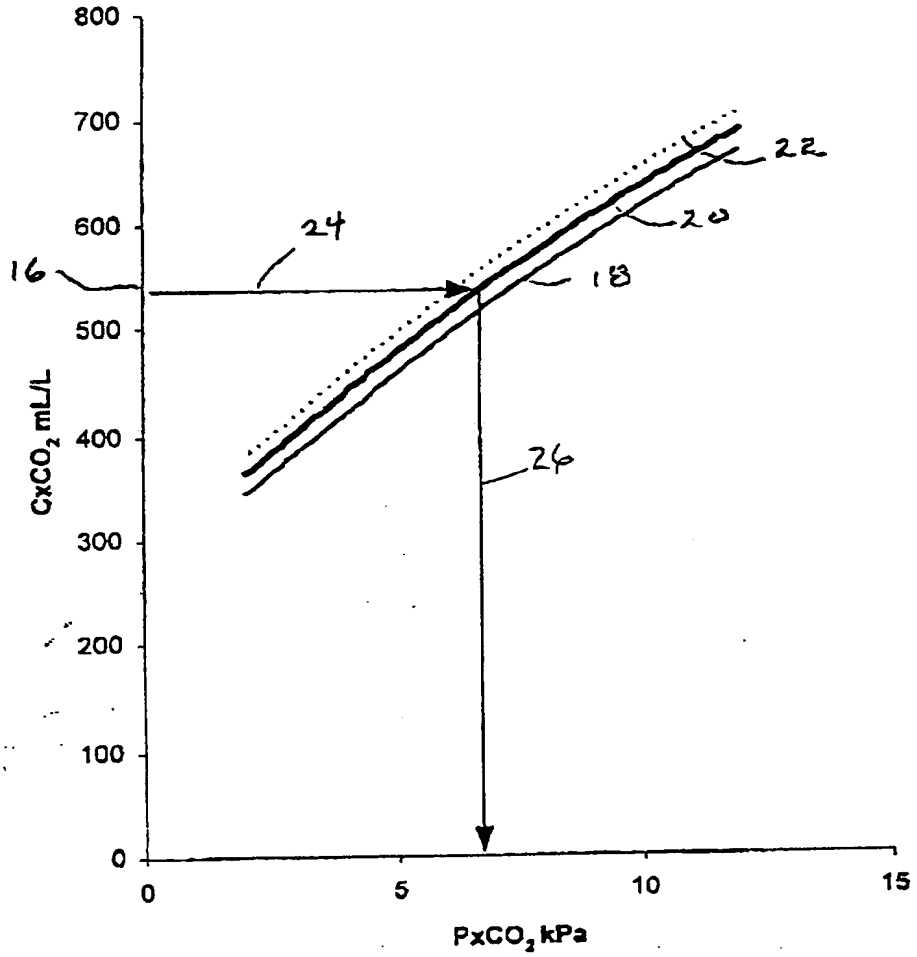
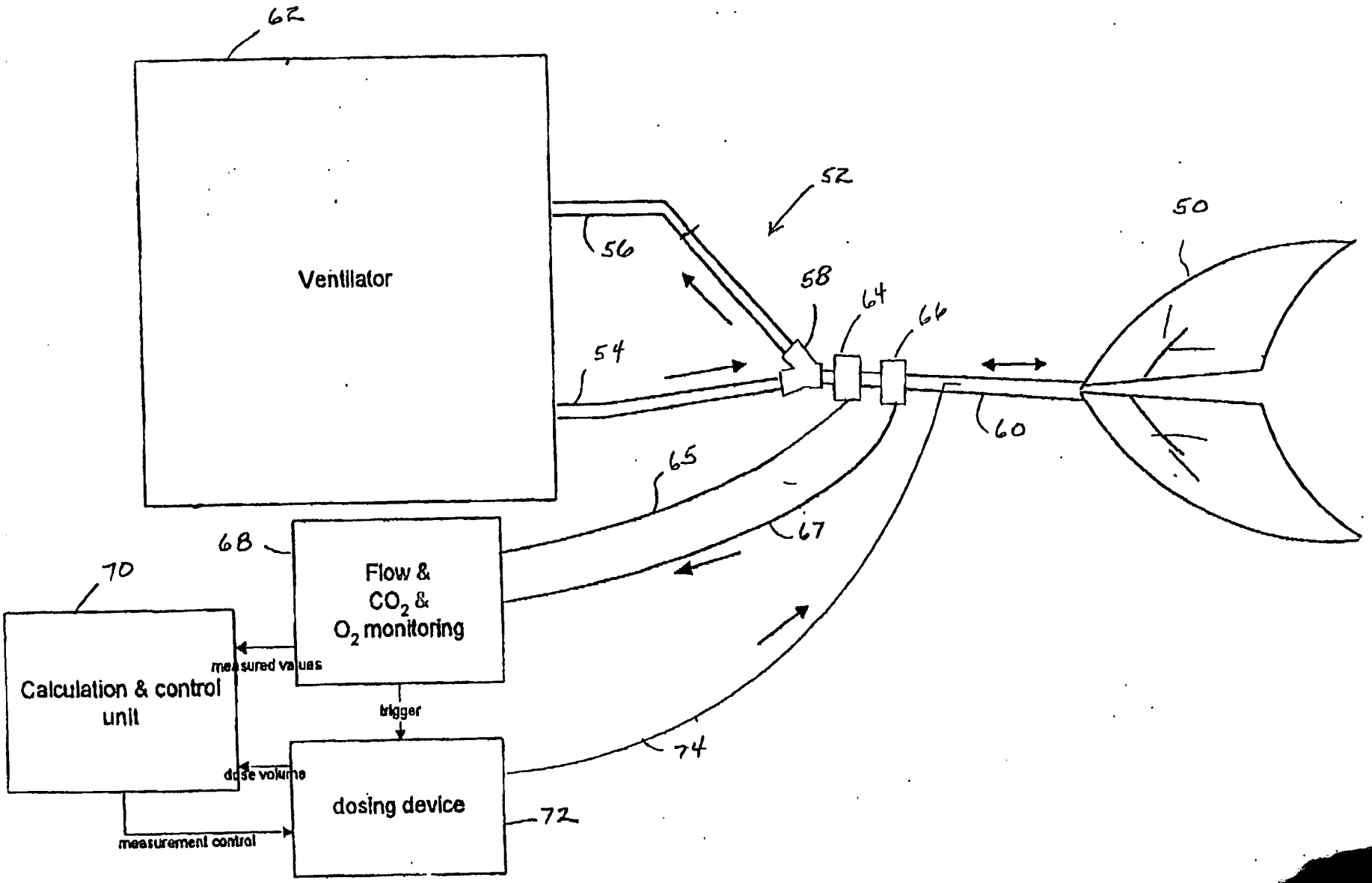


Figure 2

Figure 3


62
Ventilator
52
56
58
64
66
50
54
60
65
67
68
Flow &
CO_2 &
O_2 monitoring
70
Calculation & control unit
measured values
trigger
dose volume
dosing device
72
74
measurement control

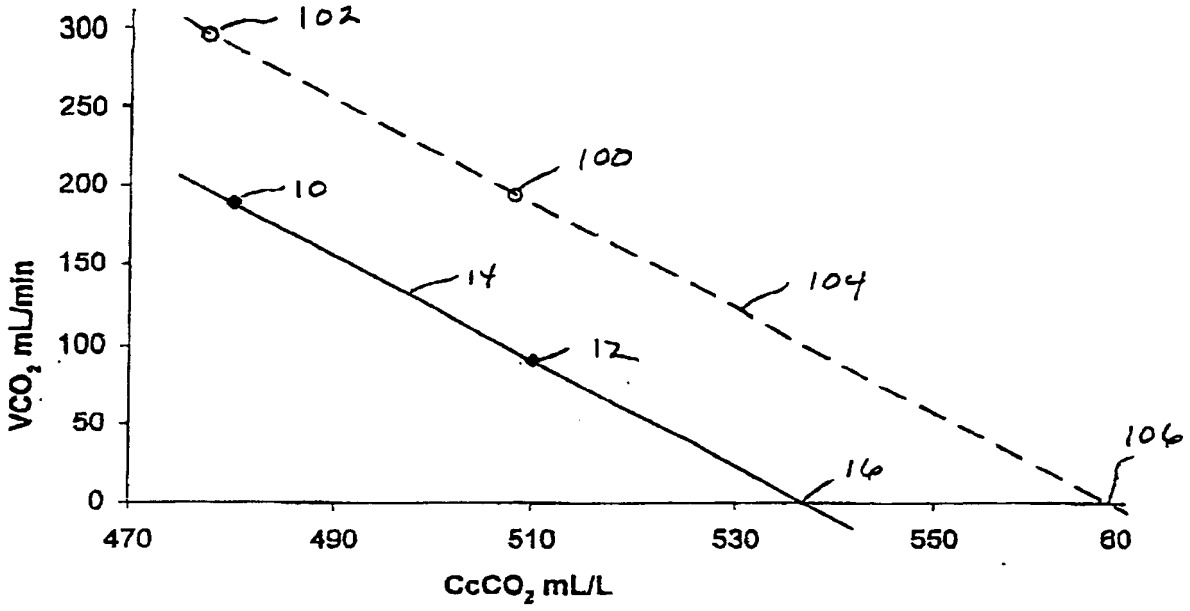

300
250
200
150
100
50
0
VCO2 mL/min
470
490
510
530
550
60
CcCO2 mL/L
102
100
10
14
12
16
104
106

Figure 4